

REMARKS

The Office Action and the cited and applied references have been carefully reviewed. No claim is allowed. Non-elected claims 11-27 are withdrawn from consideration by the examiner. Claims 1-6 and 8-10, which are directed to the elected invention, presently appear in this application along with non-elected claims 11-27, and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

Claims 1-5 and 8-10 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3, and 4 of U.S. Patent No. 6,207,641 B1.

Applicants request that this rejection be held in abeyance until such time that at least one claim is deemed allowable in this application.

Claims 1-5 and 8-10 have been rejected under 35 U.S.C. §103(a) as being obvious over claim 1 of U.S. Patent No. 6,207,641 B1 for the same reasons addressed above.

Applicants intend to submit in a supplemental response a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another".

With regard to new claim 28, it is submitted that the substitution of Cys residues as recited in claim 28 cannot be made obvious by the disclosure of U.S. Patent No. 6,207,641 B1.

Claims 1-6 and 8-10 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite for using the term "a functional equivalent". Applicants believe that this rejection is overcome by the amendment to claim 1 to define "functional equivalent". The amendment to claim 1 is supported by the specification from the middle of page 4 through page 5.

Claims 1-3, 5 and 6-10 have been rejected under 35 U.S.C. §112, first paragraph, for lack of enablement and lack of written description. The examiner states that the specification, while being enabling for claims limited in scope to an osteoclastgenic inhibitory composition, which comprises an IL-1β with SEQ ID NO:6, 7, or variants with Cys residues replaced as an effective ingredient, does not reasonably provide enablement for claims to the composition which comprises "a functional equivalent" as an effective ingredient. The examiner further states that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time

the application, was filed had possession of the claimed invention. These two rejections are respectfully traversed.

Applicants state that the term "a functional equivalent" is clearly defined in the specification from the middle of page 4 to page 8. In particular, Japanese Patent Application No. 20, 906/97 referred at page 7, line 23 discloses in detail "a functional equivalent" which is an effective ingredient of the present invention. Furthermore, various Japanese Patent Applications referred at pages 7 to 8 of the specification disclose in detail the process for producing IL-18 and "a functional equivalent" with recombinant DNA technique. The specification discloses IL-18 and "a functional equivalent" *per se*, which are effective ingredients of the present invention, including the process for producing them. Applicants therefore believe that, based on the disclosure of the specification, a person having an ordinary skill in the art would easily understand what is meant by the term "a functional equivalent" and would easily obtain "a functional equivalent".

Applicants further reemphasize that, as SEQ ID NO:7, the amino acid sequence of mouse IL-18, is provided in the specification and specifically exemplified in Experiment 6 (pages 19-24), one of skill in the art can readily align the amino acid sequences of human IL-18 (SEQ ID NO:6) and mouse

IL-18 (SEQ ID NO:7), an alignment from which the consensus sequences of SEQ ID NOs:1, 2, and 4 were identified as discussed on page 5 of the specification. From this alignment, one of skill in the art can identify the sequence homology between human IL-18 and mouse IL-18 and where sequences are conserved and where sequence conservation does not appear to be critical. Accordingly, based on the guidance provided by the teachings of functional equivalents in the specification and the amino acid alignment of two homologous IL-18s, one of skill in the art is quite enabled for the scope of functional equivalents as presently claimed.

In addition, the specification discloses in Experiment 7 at pages 24 to 35 in detail that IL-18 and "a functional equivalent" can be an effective ingredient for an osteoclastogenic inhibitory composition which bears industrial usefulness.

Reconsideration and withdrawal of the \$112, first paragraph, rejections are therefore respectfully requested.

Claims 1-6 and 8-10 have been rejected under 35 U.S.C. §102(a) as being anticipated by Ushio et al., EP 0712931A2. This rejection is respectfully traversed.

As the examiner admits at page 3, line 5 of the Office Action, Ushio discloses nothing about IL-18 and a functional equivalent thereof having an osteoclastogenic

inhibiting activity. An osteoclastgenic inhibiting activity of IL-18 and a functional equivalent thereof had not been disclosed at the time the present invention was made. It would therefore have been impossible at the time the present invention was made to expect based on prior art references an osteoclastgenic inhibiting activity of IL-18 and a functional equivalent thereof. It is the applicants' new findings that a composition comprising IL-18 or a functional equivalent thereof in an effective amount is useful as an osteoclastgenic inhibitory agent for treating and/or preventing osteoclast-related diseases. The claimed invention involves industrial usefulness as pharmaceutical.

In summary, it would have been expected even for a skilled person without the present invention that IL-18 and a functional equivalent thereof could be used for treatment and/or prevention of osteoclast-related diseases as an effective ingredient of an osteoclastgenic inhibitory agent, even if Ushio discloses a composition comprising IL-18 and a functional equivalent thereof. It is believed that the present invention had much influence on the field of the art by disclosing a new use of IL-18 and a functional equivalent thereof and opening the way to pharmaceuticals. Thus, Ushio provides neither disclosure nor suggestion about the present invention.

Moreover new claim 28, in which Cys residues are substituted cannot be anticipated by Ushio et al.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 1-3, 6, and 8 have been rejected under 35 U.S.C. §102(e) as being anticipated by Okamura et al., U.S. Patent No. 5,912,324. This rejection is respectfully traversed.

Like Ushio et al., Okamura et al. disclose only a composition comprising IL-18. Okamura teaches nothing about applicants' new findings that IL-18 and a functional equivalent thereof reveal an osteoclast inhibiting activity. Okamura suggests nothing about an osteoclastgenic inhibitory agent of the present invention which comprises IL-18 and/or a functional equivalent thereof in an effective amount.

In summary, it would have never been expected even for a skilled person without the present invention that IL-18 and a functional equivalent thereof could be used for treatment and/or prevention of osteoclast-related diseases as an effective ingredient of an osteoclastgenic inhibitory agent. It is believed that the present invention had much influence on the field of the art by disclosing a new use of IL-18 and a functional equivalent thereof and opening the way to pharmaceuticals.

As discussed above, new claim 28, in which Cys residues are substituted cannot be anticipated by Okamura et al.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, applicants submit that the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

Claims 1-3 have been amended as follows:

1 (Twice-amended). An osteoclastgenic inhibitory composition for treating and/or preventing osteoclast-related diseases, which comprises a pharmaceutically-acceptable carrier and, as an active ingredient, an effective amount of an interleukin-1 $\beta$  comprising the amino acid sequence of SEQ ID NO:6 and/or a functional equivalent thereof ~~as an effective ingredient~~, said interleukin-1 $\beta$  or ~~a~~ and said functional equivalent thereof being capable of exerting osteoclastgenic inhibitory activity, wherein said functional equivalent is a member selected from the group consisting of (i) those wherein one or more amino acids in the amino acid sequence of interleukin-1 $\beta$  are replaced with different amino acids, (ii) those wherein one or more amino acids are added to the N- and/or C-termini of the amino acid sequence of interleukin-1 $\beta$ , (iii) those wherein one or more amino acids are inserted into the internal sites of the amino acid sequence of interleukin-1 $\beta$ , (iv) those wherein one or more amino acids in the N- and/or C-terminal regions of the amino acid sequence of interleukin-1 $\beta$  are deleted, and (v) those wherein one or more amino acids in the internal regions of the amino acid sequence of interleukin-1 $\beta$  are deleted.

2 (Twice-amended). The inhibitory composition of claim 1, wherein said interleukin-18 or ~~a~~ said functional equivalent thereof comprises each of the amino acid sequences of SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3.

3 (Twice-amended). The inhibitory composition of claim 1, wherein said interleukin-18 or ~~its~~ functional equivalent thereof comprises both the amino acid sequences of SEQ ID NO:4 and SEQ ID NO:5.